REMARKS

The specification is amended to correct a typographical error. The Abstract is also amended.

Claims 1, 5 and 17 are amended herein. Claims 10-13 and 18-19 are canceled herein. Claims 15-16 and 20-21 were previously canceled. New claim 22 is added.

Support for the claim amendments is found, for example, at page 14, line 35 to page 15, line 1. No new matter is presented.

Upon entry of the Amendment claims, 1-9, 14, 17 and 22 will be all of the claims pending in the application.

I. Restriction/Election

The Examiner has acknowledged Applicant's election filed on January 8, 2008 of Group I including claims 1-14 and 17. The Examiner indicates that claims 15, 16, 18 and 19 are withdrawn from consideration. However, claims 15-16 were canceled in the Response to Restriction filed January 8, 2008 and therefore should be indicated as being "canceled" instead of "withdrawn".

II. Response to Objection to Specification

On page 2 of the Action, the Examiner objects to the Abstract of Disclosure for referring to non-elected subject matter.

The Abstract is replaced herein with a new Abstract, which does not refer to the method of preparation of the pharmaceutical composition.

Accordingly, Applicants respectfully request withdrawal of the objection to the specification.

III. Response to Claim Objections

On pages 2-3 of the Action, the Examiner objects to claims 10 and 11 under 37 C.F.R. § 1.75(c) as being in improper dependent form for failing to further limit the subject matter of claim 1.

On page 3 of the Action, claim 9 is objected to by the Examiner because of the misspelling of "glycin". The Examiner has requested correction to "glycine".

Claims 10 and 11 are canceled herein, thereby rendering this objection moot.

Claim 9 is amended herein to correct the misspelled word "glycin", thereby obviating this objection.

Accordingly, Applicants respectfully request withdrawal of the objections to the claims.

IV. Response to Claim Rejections Under 35 U.S.C. § 112

A. Written Description

On pages 3-4 of the Action, claims 1-14 and 17 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner states that the terms "compound", "proton-coupled transporter" and "pH-sensitive polymer" are mentioned in the specification, but are not defined or related to one another in a clear and concise manner.

Applicants respectfully traverse the rejection on the basis that each of these terms is specifically defined in the present specification and the relationship is clear based on the description.

The term "proton-coupled transporter" is defined at page 7 of the specification as "active transporters that transport substrates from the mammalian gastrointestinal tract into cells by taking advantage of the proton (H+) gradient". It is further described that proton-coupled transporters are expressed within the gastrointestinal tract and the like, and, specifically, adjacent to the surface of the brush border membranes of the gastrointestinal tract (especially, the surface of the brush border membranes of small-intestinal epithelial cells). Also, it is disclosed that they are influx transporters actively transporting nutrients and medicaments into cells. See page 7, lines 1-13. Additionally, specific examples of the proton-coupled transporters are described at page 7, line 14 to page 8, line 4.

"Compounds recognized by proton-coupled transporters" are defined at page 8 of the specification as "substrates" and "compounds that can be recognized by the aforementioned proton-coupled transporters and taken up into cells (e.g., small-intestinal epithelial cells) from the gastrointestinal tract." A method for determining whether or not a compound can be recognized by the proton-coupled transporter is described at page 8, line 10 to page 9, line 22. Further, examples of specific compounds recognized by specific types of proton-coupled transporters are provided at page 9, line 25 to page 11, line 2. Additionally, the relationship between the compounds and the proton-coupled transporters is clear as the compounds are recognized by the proton-coupled transporters.

"pH-sensitive polymers" are described at page 13 of the specification as polymers that release protons depending upon the pH of the specific site of a living body (e.g., gastrointestinal tract), for example, polymers that dissolve or swell by releasing protons under high pH conditions. Further, specific examples are provided at page 13, lines 24-34.

Also, it is disclosed in the present specification that the pharmaceutical preparation is prepared by mixing a pH-sensitive polymer with a compound recognized by a proton-coupled transporter. See, e.g., page 14, lines 8-10. Thus, the relationship between the "compound recognized by a proton-coupled transporter" and the "pH-sensitive polymer" as components of the pharmaceutical composition is clear.

B. §112, Second Paragraph

At pages 4-6 of the Action, claims 1-14 and 17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as follows.

1. "a compound recognized by a proton-coupled transporter and a pH-sensitive polymer"

The Examiner states that the recitation of "a compound recognized by a proton-coupled transporter and a pH-sensitive polymer" is not clear, allegedly because it is uncertain whether the pH-sensitive polymer recognizes the compound of the composition or if the pH-sensitive polymer is part of the actual composition. For purposes of examination, the Examiner considers the claims to mean a composition comprising (a) a compound which is recognized by a proton-coupled transporter; and (b) a pH-sensitive polymer.

Applicants note that the Examiner's interpretation of the claim language is correct as supported by the description at page 14, lines 8-10, which describes that the pharmaceutical preparation is prepared by mixing a pH-sensitive polymer with a compound recognized by a proton-coupled transporter as mentioned above. To further clarify the claim language, claims 1

and 17 are amended herein by identifying the components of the composition as component (a) and component (b).

Accordingly, Applicants respectfully request withdrawal of this ground for rejection.

2. "excellent"

The Examiner states that the term "excellent" in claim 1 is a relative term and renders the claim indefinite. The Examiner also states that this term renders the parameter "gastrointestinal absorbability" indefinite.

Claim 1 is amended herein by deleting the term "excellent", thereby obviating the rejection.

Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

3. "comprising a compound recognized by a proton-coupled transporter and a pH-sensitive polymer"

The Examiner states that the recitation of a compound "comprising a compound recognized by a proton-coupled transporter and a pH-sensitive polymer" is not clear, allegedly because it is not certain whether the pH-sensitive polymer is part of the compound doing the recognizing or a part of the compound being recognized.

Applicants submit that it is clear that the compound recognized by a proton-coupled transporter is a component of the pharmaceutical preparation which is distinct from the pH-sensitive polymer for the reasons set forth above. Thus the amendment to claims 1 and 17 is believed to clarify this point.

Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

4. "optimum"

The Examiner states that the term "optimum" is a relative term which renders the claims indefinite, and that the term renders vague and indefinite the amount of the pH-sensitive polymer sufficient to effect cellular uptake of the compound. For purposes of examination, the Examiner interprets this term to mean that any amount of a pH-sensitive polymer need only be present in the compound to "optimally" enable cellular uptake of the compound.

Claims 1 and 17 are amended herein to recite that the amount of the pH-sensitive polymer is 5 to 40 wt% based on the weight of the entire pharmaceutical preparation. Applicants submit that one of ordinary skill in the art would be able to select the amount of the pH-sensitive polymer from the range of 5 to 40 weight % to adjust the pH of the gastrointestinal tract at which the proton-coupled transporter optimally functions for cellular uptake of the compound. Thus, the meaning and scope of the claims is clear.

Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

5. The compound recognized by the amino acid transporter in claim 9

The Examiner asserts that the limitation to the compound recognized by the amino acid transporter in claim 9 is unclear as to the number of members recognized and whether either or both of "L-alanine" and "-alanine" are within the intended scope.

Claim 9 is amended herein to correct the typographical error in claim 9 by replacing the term "-alanine" with "ß-alanine". Applicants submit that the amendment to claim 9 clarifies the intended scope of the claim.

Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

6. Eudragit recited in claim 13

The Examiner states that claim 13 contains the trademark/trade name "Eudragit" which renders the scope of the claim uncertain because a trademark or tradename cannot be properly used to identify any particular material or product, as a trademark or trade name identifies the source of the goods and not the goods themselves. The Examiner also states that if claim 12 is found allowable, claim 13 will be objected to as a substantial duplicate of claim 12.

Claim 13 is canceled herein, thereby obviating the rejection.

Accordingly, Applicants respectfully request withdrawal of this rejection.

V. Response to Claim Rejections Under 35 U.S.C. § 102

A. Behl et al

On page 7 of the Action, claims 1-7, 12-14 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Behl et al (US 4,525,339).

Applicants respectfully traverse the rejection.

The present invention is directed to a composition comprising (a) a compound recognized by a proton-coupled transporter; and (b) a pH-sensitive polymer.

Behl et al teaches an orally administered enteric coated pharmaceutical composition which consists essentially of a beta-lactam antibiotic admixed with an enhancer consisting of a C_2 to C_{12} glyceride mixture with fatty acids having a length of C_2 to C_{12} (claim 1). Examples of C_2 to C_{12} fatty acids admixed with glycerides that are taught include butyric acid (col. 10, lines 20-30). Table 3 also teaches the use of monoglyceride of acetic acid (e.g., Enteral monoacetin). Enteric coatings that are taught include methacrylic acid copolymer L and S (e.g., Eudragit L and S) (col. 10, lines 58-65; col. 11, lines 1-30).

The Examiner believes that Behl discloses compounds such as ß-lactam antibiotics that are recognized by the proton-coupled transporter, and, moreover, that Behl discloses enteric coating materials.

However, Behl does not teach or suggest the specific combination of ß-lactam antibiotics and a pH-sensitive polymer. Therefore, Behl does not disclose all of the features of the present invention and cannot be said to anticipate the present claims within the meaning of §102.

Accordingly, Applicants respectfully request withdrawal of the §102 rejection.

B. Gaunt

On page 8 of the Action, claims 1-3, 8, 9, 12-14 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gaunt (US 3,148,124).

Applicants respectfully traverse the rejection.

The Examiner states that Gaunt discloses an orally administered agent containing water-soluble medicaments and at least one water-insoluble material such as glycine. The Examiner further states that Gaunt describes a pH-sensitive polymer (a polymethacrylic acid, etc.) that can be used as an alkali sensitive material in combination with drugs (column 5, lines 39-52).

However, Gaunt does not specifically disclose the combination of compounds recognized by the proton-coupled transporter and pH-sensitive polymer as recited in amended claim 1. Thus, Gaunt does not anticipate the present claims within the meaning of § 102.

Accordingly, Applicants respectfully request withdrawal of the §102 rejection.

VII. Response to Claim Rejections Under 35 U.S.C. § 103

At pages 9-10 of the Action, claims 1-9, 12-14 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Behl et al in view of Gaunt.

Applicants respectfully traverse the rejection.

Claim 1 is drawn to an orally-administered, gastrointestinally-absorbed, pharmaceutical preparation.

Behl et al merely discloses Eudragit as one of the components of the coating agent, and nowhere mentions the adjustment of a pH value in the gastrointestinal tract to enhance the incorporation of ß-lactam antibiotics into the cell. Gaunt only discloses that the polyacrylic acid derivatives are used to control the release of drugs by digestive fluids (col. 5, lines 39-52).

On the other hand, the pH-sensitive polymer of the present invention is to be used to impart to the gastrointestinal tract a pH at which the proton-coupled transporter optimally functions for cellular uptake of the compound recognized by the proton-coupled transporter. Neither of the cited references recognizes the problem to be solved by the present invention.

Further, according to the amended claims, the pH-sensitive polymer is limited to "at least one species selected from the group consisting of dried methacrylic acid copolymer, methacrylic acid copolymer LD, methacrylic acid copolymer L, methacrylic acid copolymer S, polyacrylic acid maleic acid/n-alkyl vinyl ether copolymer, hydroxypropylmethylcellulose acetate succinate, and hydroxypropylmethylcellulose phthalate". The amount of the pH-sensitive polymer is also limited to 5 to 40 wt% based on the weight of the entire pharmaceutical preparation. Neither of the cited references teaches or suggests these features of the present invention in combination.

In addition, the present invention is not only a new composition, but also a product that can solve the problems of low absorption of orally administered preparations due to low membrane permeability or instability in the gastrointestinal tract.

More specifically, the subject matter defined in Claim 1 provides the following notable effects.

(i) It increases gastrointestinal absorption of compounds recognized by a proton-coupled transporter.

(ii) Unlike existing pharmaceutical compositions, it significantly increases gastrointestinal absorption even in the lower gastrointestinal tract, where the amount of protons is reduced.

(iii) It improves the gastrointestinal absorption of substrates that have a tendency to be poorly absorbed (a high bioavailability is obtained).

(iv) Moreover, the present invention provides a pharmaceutical preparation that ensures a desirable pH environment in the organ (intestinal tract, etc.) where the compound recognized by the proton-coupled transporter is absorbed.

These advantageous effects of the present invention are not recognized by the cited references. Thus, one of ordinary skill in the art would not have had a reasonable expectation of achieving the claimed invention based on the cited references, whether taken alone or in combination. For at least these reasons the present invention is not rendered obvious.

Additionally, Applicants submit that the present invention provides unexpectedly superior results of significant improvements in gastrointestinal absorption of the compounds of the invention when combined with the pH-sensitive polymers of the invention as evidenced by data provided in the specification, such as a comparison of the results of Examples 3 and 4 in the specification. Portions of Examples 3 and 4 and Table 1 in the specification are reproduced below.

Example 3 (page 20, line 1 to page 21, line 4 of the English specification of the present invention):

To investigate whether gastrointestinal absorption in rats of β-lactam antibiotics under physiological conditions can be improved by controlling the gastrointestinal pH, absorption of a zwitterionic compound (CDX) and an anionic compound (CFIX) in the presence and absence of a pH-sensitive polymer (Eudragit L100-55) was examined using the *in situ* closed loop method (Figure 6 shows a diagram).

As shown in Figure 3A, absorption of CDX containing no Eudragit L100-55 was about 40%. However, a significant increase was observed from the use of Eudragit L100-55 in a proportion of 20 wt.%, resulting in CDX absorption of about 80%. Moreover, gastrointestinal pH decreased as Eudragit L100-55 was added (Figure 3B).

In contrast, CFIX was barely absorbed by the rat ileum (Figure 3C). However, as with CDX, the use of Eudragit L100-55 in a proportion of 20 wt.% significantly improved the CFIX absorption, to about 35%. The pH of the fluid in the gastrointestinal tract was decreased by Eudragit L100-55 (Figure 3D).

Example 4 (page 21, line 6 to page 22, line 14 of the English specification of the present invention):

To investigate whether absorption of orally-administered peptidergic compounds in rats is improved by controlling gastrointestinal pH using pH-sensitive polymers, the time course of the plasma concentration of CFIX was examined after orally administering the peptidergic compound CFIX in combination with a pH-sensitive polymer (Eudragit L100-55) or a pH-insensitive polymer (Eudragit RS PO).

As shown in Table 1, when CFIX and Eudragit RS PO, as a pH-insensitive polymer, were administered simultaneously, no meaningful differences from the administration of CIFX alone were observed in the blood concentration-time curve area under the plasma drug concentration-

time curve (AUC), the maximum plasma drug concentration observed in the plasma following administration of an extravascular dose (Cmax), or the time at which the highest drug concentration occurs following administration of an extravascular dose (Tmax). Also, no change was observed in the absorption of orally administered CFIX.

However, when CFIX and pH-sensitive acidic Eudragit L100-55 were simultaneously administered, significant increases were observed in AUC and Cmax compared with the control containing no polymer, resulting in a substantial increase in the absorption of orally administered CFIX.

Table 1 (at page 23 of the specification)

Sample	$AUC_{0\text{-}8h}$(μg.hr/mL)	Cmax (μg/mL)	Tmax (hr)
Control	**10.81 ± 1.48**	**4.13±0.50**	**0.72±0.20**
Eudragit L100-55	**27.60±2.39[a]**	**11.52 ± 1.86[a]**	**1.20±0.20**
Eudragit L100-55 +CDX 2 mM	**24.24 ± 4.20**	**6.39 ± 0.88[b]**	**1.00 ±0.00**
Eudragit L100-55 +CDX 10 mM	**11.52 ± 0.99[b]**	**3.40 ± 0.60[b]**	**1.43± 0.20**
Eudragit RS PO	**8.83 ± 0.28**	**3.39± 0.16**	**1.00±0.00**

Each data represents the mean ± S.E.M. of three experiments at least.
[a]Significantly different from the corresponding control value at $p < 0.05$.
[b]Significantly different from the corresponding Eudragit L100-55 values at $p < 0.05$.

According to the above disclosure, it is clear that the pharmaceutical composition of the present invention significantly enhances the gastrointestinal absorption of compounds recognized by a proton-coupled transporter. For this additional reason the present invention is patentable over the cited references.

Accordingly, claim 1 is novel and unobvious over the cited references.

Claims 2 to 9 and 14 directly, or indirectly, depend from claim 1. According to the above, claim 1 is novel and unobvious over the cited references, and therefore, these dependent claims, i.e., claims 2 to 9 and 14, are also novel and unobvious over the cited references for at least the same reasons. Claim 17 recites a pharmaceutical preparation for enhancing gastrointestinal absorbability of a compound recognized by a proton-coupled transporter as having technical features as described in claim 1, and therefore, claim 17 is also novel and unobvious over the references for at least the same reasons. Claim 18 depends from claim 1 or claim 17. Therefore, claim 18 is also novel and unobvious for at least the same reasons.

Accordingly, withdrawal of the §103 rejection is respectfully requested.

VIII. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

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